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(71) Applicant *(for all designated States except US)*: SMITH-KLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : SANGER, Gareth, John [GB/GB]; WARDLE, Kay, Alison [GB/GB]; Smith-Kline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB).

(74) Agent: JONES, Pauline; SmithKline Beecham, Corporate Patents, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB).

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(54) Title: USE OF 5-HT4 MODULATORS FOR THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT OF THE BLADDER DISEASES

(57) Abstract

A compound which acts as an antagonist at $5\text{-}HT_4$ receptors is of potential use in the treatment of conditions associated with bladder hypersensitivity, such as urinary incontinence, which is often associated with irritable bowel syndrome (IBS) and a compound which acts as an agonist at $5\text{-}HT_4$ receptors is of potential use in the treatment of conditions associated with a poorly functioning bladder, such as urinary bladder hypoactivity following prostectomy.

Use of 5-HT4 modulators for the manufacture of a
medicament for the treatment of the bladder diseases

This invention relates to treatment of conditions associated with bladder
5   hypersensitivity, and conditions associated with a poorly functioning bladder.

European Journal of Pharmacology 146 (1988), 187-188, and Naunyn-
Schmiedeberg's Arch. Pharmacol. (1989) 340:403-410, describe a non
classical 5-hydroxytryptamine receptor, now designated the $5\text{-}HT_4$ receptor,
10   and that tropisetron (ICS 205-930), which is also a $5\text{-}HT_3$ receptor antagonist,
acts as an antagonist at this receptor and metoclopramide is an agonist at
this receptor.

WO 91/16045 (SmithKline and French Laboratories Limited) describes the
15   use of cardiac $5\text{-}HT_4$ receptor antagonists in the treatment of atrial
arrhythmias and stroke.

Metoclopramide has been shown to be effective in treating a poorly
functioning bladder, (Scand. J. Urology and Nephrology, 13:79-82 (1979) but
20   this has not been specifically linked to any known action of metoclopramide.

There are reports in the literature of $5\text{-}HT_4$ receptors potentiating contractions
in human bladder (Br. J. Pharmacol, 61, 115P) and inhibiting contractions in
monkey bladder (2nd International Symposium on Serotonin, Houston,
25   September 1992, page 86).

We have now discovered that a compound which acts as an antagonist at
$5\text{-}HT_4$ receptors is of potential use in the treatment of conditions associated
with bladder hypersensitivity, such as urinary incontinence, which is often
30   associated with irritable bowel syndrome (IBS) and a compound which acts
as an agonist at $5\text{-}HT_4$ receptors is of potential use in the treatment of
conditions associated with a poorly functioning bladder, such as urinary
bladder hypoactivity following prostectomy. When used herein the term
'$5\text{-}HT_4$ modulator' is used to denote antagonists and agonists.
35

The invention therefore provides a method for the treatment and/or
prophylaxis of conditions associated with bladder hypersensitivity and
conditions associated with a poorly functioning bladder in mammals, including

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humans, which method comprises administering to the mammal in need of such treatment and/or prophylaxis, an effective and/or prophylactic amount of a 5-HT$_4$ modulator.

5   5-HT$_4$ modulators may be identified according to standard methods, such as those described hereinafter, and that described in Naunyn-Schmiedeberg's Arch Pharmacol. 342, 619-622.

Examples of 5-HT$_4$ receptor antagonists include ICS 205-930 (tropisetron -
10   Sandoz), R 50 595 (Janssen), which is described in FR 76530 and Eur.J. Pharmacol., 181 119-125 (1990), and SDZ 205-557, which is described by K.H. Buchheit and R. Gamse in Naunyn-Schmiedeberg's Arch. Pharmacol., 343 (Suppl.), R101 (1991). DAU 6285 (Naunyn-Schmiedeberg's Arch. Pharmacol, 345; 264-269 (1992) and RS 23597-190 (Syntex - British
15   Pharmacology Society Meeting, September 1992).

EP-A-501322 (Glaxo Group Limited) describes indole derivatives having 5-HT$_4$ receptor antagonist activity and reports 5-HT$_4$ receptors are believed to be associated with conditions involving *inter alia* the urinary tract (e.g.
20   urinary incontinence).

Examples of 5-HT$_4$ receptor agonists include cisapride, renzapride and zacopride.

25   In one aspect, the 5-HT$_4$ modulator is more potent at 5-HT$_4$ receptors than at 5-HT$_3$ receptors.

Preferably, the 5-HT$_4$ modulator is in substantially pure pharmaceutically acceptable form.
30
The administration of the 5-HT$_4$ modulator may be by way of oral, sublingual, transdermal or parenteral administration.

An amount effective to treat the disorder hereinbefore described depends on
35   the usual factors such as the nature and severity of the disorder being treated and the weight of the mammal. However, a unit dose will normally contain 0.1 to 50 mg for example 0.5 to 10 mg, of the 5-HT$_4$ modulator. Unit doses will normally be administered once or more than once a day, for example 2, 3,

or 4 times a day, more usually 1 to 3 times a day, such that the total daily
dose is normally in the range, for a 70 kg adult of 0.1 to 50 mg, for example
0.1 to 5 mg, that is in the range of approximately 0.001 to 1 mg/kg/day, more
usually 0.005 to 0.2 mg/kg/day.

5

For oral or parenteral administration, it is greatly preferred that the 5-HT$_4$
modulator is administered in the form of a unit-dose composition, such as a
unit dose oral or parenteral composition.

10   Such compositions are prepared by admixture and are suitably adapted for
oral or parenteral administration, and as such may be in the form of tablets,
capsules, oral liquid preparations, powders, granules, lozenges,
reconstitutable powders, injectable and infusable solutions or suspensions or
suppositories.

15

Tablets and capsules for oral administration are usually presented in a unit
dose, and contain conventional excipients such as binding agents, fillers,
diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings,
and wetting agents. The tablets may be coated according to well known
20   methods in the art.

Suitable fillers for use include cellulose, mannitol, lactose and other similar
agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch
derivatives such as sodium starch glycollate. Suitable lubricants include, for
25   example, magnesium stearate. Suitable pharmaceutically acceptable wetting
agents include sodium lauryl sulphate.

These solid oral compositions may be prepared by conventional methods of
blending, filling or tabletting. Repeated blending operations may be used to
30   distribute the active agent throughout those compositions employing large
quantities of fillers. Such operations are, of course, conventional in the art.

Oral liquid preparations may be the form of, for example, aqueous or oily
suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as
35   a dry product for reconstitution with water or other suitable vehicle before use.
Such liquid preparations may contain conventional additives such as
suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin,
hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or

hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example
5 methyl or propyl $\underline{p}$-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Oral formulations also include conventional sustained release formulations, such as tablets or granules having an enteric coating.
10

For parenteral administration, fluid unit dose forms are prepared containing the 5-HT$_4$ modulator and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a
15 vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.
20

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included
25 in the composition to facilitate uniform distribution of the compound of the invention.

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the treatment concerned.
30

The present invention also provides the use of a 5-HT$_4$ modulator in the manufacture of a medicament for use in the treatment and/or prophylaxis of conditions associated with a poorly functioning bladder and bladder hypersensitivity. Such treatment and/or prophylaxis may be carried out as
35 hereinbefore described.

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The present invention further provides a pharmaceutical composition for use in the treatment and/or prophylaxis of conditions associated with a poorly functioning bladder and bladder hypersensitivity, which comprises a 5-HT$_4$ modulator, and a pharmaceutically acceptable carrier. Such compositions

5   may be prepared in the manner as hereinbefore described.

5-HT$_4$ modulator activity

10

1)   Guinea pig colon

Male guinea-pigs, weighing 250-400g are used. Longitudinal muscle-myenteric plexus preparations, approximately 3cm long, are obtained from

15   the distal colon region. These are suspended under a 0.5g load in isolated tissue baths containing Krebs solution bubbled with 5% CO_2 in O_2 and maintained at 37°C. In all experiments, the Krebs solution also contains methiothepin 10^{-7}Mn and granisetron 10^{-6}M to block effects at 5-HT$_1$, 5-HT$_2$ and 5-HT$_3$ receptors.

20

After construction of a simple concentration-response curve with 5-HT, using 30s contact times and a 15min dosing cycle, a concentration of 5-HT is selected so as to obtain a contraction of the muscle approximately 40-70% maximum(10-9M approx). The tissue is then alternately dosed every 15min

25   with this concentration of 5-HT and then with an approximately equi-effective concentration of the nicotine receptor stimulant, dimethylphenylpiperazinium (DMPP). After obtaining consistent responses to both 5-HT and DMPP, increasing concentrations of a putative 5-HT$_4$ modulator are then added to the bathing solution. The effects of this compound are then determined as a

30   percentage reduction of the contractions evoked by 5-HT or by DMPP.

From this data, IC$_{50}$ values are determined, being defined as the concentration of antagonist or agonist which reduces or increases the contraction by 50%. A compound which reduces the response to 5-HT but

35   not to DMPP is believed to act as a 5-HT$_4$ receptor antagonist and a compound which increases the response to 5-HT but not to DMPP is believed to act as a 5-HT$_4$ receptor agonist.

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2) Rat oesophagus

Rat oesophageal tunica muscularis mucosae is set up according to Baxter *et. al.* Naunyn-Schmiedeberg's Arch. Pharmacol., 343, 439-446 (1991). The inner smooth muscle tube of the muscularis mucosae is isolated and mounted for isometric tension recording in oxygenated (95% O_2/5% CO_2) Tyrodes solution at 37°C. All experiments are performed in pargyline pre-treated preparations (100μM for 15 min followed by washout) and in the presence of cocaine (30μM). Relaxant responses to 5-HT are obtained after pre-contracting the oesophagus tissue with carbachol (3μM).

Claims

1.   A method for the treatment and/or prophylaxis of conditions associated with bladder hypersensitivity and conditions associated with a poorly functioning bladder in mammals, including humans, which method comprises administering to the mammal in need of such treatment and/or prophylaxis, an effective and/or prophylactic amount of a 5-HT$_4$ modulator.

2.   The use of a 5-HT$_4$ modulator in the manufacture of a medicament for use in the treatment and/or prophylaxis of conditions associated with a poorly functioning bladder and bladder hypersensitivity.

3.   A pharmaceutical composition for use in the treatment and/or prophylaxis of conditions associated with a poorly functioning bladder and bladder hypersensitivity, which comprises a 5-HT$_4$ modulator, and a pharmaceutically acceptable carrier.

4.   A method, use or composition according to claim 1, 2 or 3 wherein the 5-HT$_4$ modulator is a 5-HT$_4$ receptor antagonist.

5.   A method, use or composition according to claim 4 for the treatment of urinary incontinence.

6.   A method, use or composition according to claim 5 for the treatment of urinary incontinence associated with irritable bowel syndrome.

7.   A method, use or composition according to claim 4, 5 or 6 wherein 5-HT$_4$ receptor antagonist is R 50 595, SDZ 205-557, DAU 6285, RS 23597-190 or a compound described in relation to EP-A-501322 (Glaxo Group Limited).

8.   A method, use or composition according to claim 1, 2 or 3 wherein the 5-HT$_4$ modulator is a 5-HT$_4$ receptor agonist.

9.   A method, use or composition according to claim 8 for the treatment of urinary bladder hypoactivity following prostectomy.

10.   A method, use or composition according to claim 8 or 9 wherein 5-HT$_4$ receptor agonist is cisapride, renzapride or zacopride.

I. CLASSIFICATION F SUBJECT MATTER   (If several classification symbols apply, indicate all)[6]
According to International Patent Classification (IPC) or to both National Classification and IPC
Int.Cl. 5 A61K31/40;   A61K31/445;   A61K31/435

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category[o]	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
P,X	EP,A,0 501 322 (GLAXO GROUP LTD) 2 September 1992 cited in the application see page 5, line 18 - line 37; claims 1-16 ---	1-7
P,X	EP,A,0 467 365 (E.R.SQUIBB & SONS, INC.) 22 January 1992 see page 2, line 49 - page 3, line 56 ---	1-3,8-10
X	PARAPLEGIA vol. 26, no. 3, 1988, pages 162 - 164; M.ETIENNE ET AL.: 'Treatment with cisapride of the gastrointestinal and urological sequelae of spinal cord transection: case report' see conclusion see abstract --- -/-	1-3,8-10

° Special categories of cited documents:[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member ·· the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
15 MARCH 1993	06. 04. 93.

International Searching Authority	Signature of Authorized Officer
EUROPEAN PATENT OFFICE	TZSCHOPPE D. A.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		Relevant to Claim No.
Category°	Citation of Document, with indication, where appropriate, of the relevant passages	
X	PARAPLEGIA vol. 26, no. 3, 1988, pages 159 - 161; G.H. DE GROOT ET AL.: 'Effects of cisapride on constipation due to neurological lesion' see discussion see abstract ---	1-3,8-10
X	ACTA BELG. MED. PHYS. vol. 12, no. 3, 1989, pages 81 - 88; P.HANSON ET AL.: 'Effet du cisapride sur les vessies neurologiques' see conclusions ---	1-3,8-10
P,X	DRUG. DEV. RES. vol. 27, no. 4, 1992, pages 361 - 375; WILLIAM D. STEERS ET AL.: 'Effects of serotonic agonists on micturation and sexual function in the rat' see abstract ---	1-3,8-10
A	DRUGS FUTURE vol. 16, no. 11, 1991, pages 1011 - 1026; M. TURCONI ET AL: 'Azabicycloalkyl benzimidazolones: Interaction with serotonergic 5-HT3 and 5-HT4 receptors and potential therapeutic implications' see the whole document ---	1-10

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0501322	02-09-92	AU-A-	1209492	15-09-92
		WO-A-	9214727	03-09-92
EP-A-0467365	22-01-92	CA-A-	2044854	20-01-92
		JP-A-	4234328	24-08-92

« 9 »

Pathogenesis and Management of the Irritable Bowel Syndrome

W. Grant Thompson

There is no pathophysiologic marker for the functional gastrointestinal (GI) syndromes. Therefore, we must rely on symptoms for their definition and classification. A series of international working teams [1–3] meeting in Rome developed a classification of these disorders and offered definitions and research criteria for each syndrome (Table 9.1). The irritable bowel syndrome (IBS) is distinct from other functional bowel disorders such as functional constipation and functional diarrhea (Table 9.2). The symptom criteria for the IBS are known as the Rome criteria and are shown in Table 9.3. Subjects with functional bowel symptoms that are insufficient to be classified as the IBS or as one of the other syndromes listed in Table 9.2 are said to have an unspecified functional bowel disorder. These disparate syndromes are likely to have different causes and require different tests and treatments.

Table 9.1 Definitions. (From Thompson *et al.* [3].)

A functional gastrointestinal disorder
'A variable combination of persistent or recurrent gastrointestinal symptoms not explained by structural or biochemical abnormalities. These may include symptoms attributable to the oropharynx, oesophagus, stomach, biliary tree, small or large intestine or anus.'

A functional bowel disorder
'A functional gastrointestinal disorder with symptoms attributable to the mid or lower intestinal tract. The symptoms include abdominal pain, bloating or distension and various symptoms of disordered defecation.'

The irritable bowel syndrome
'A functional bowel disorder in which abdominal pain is associated with defecation or a change in bowel habit, and with features of disordered defecation and with distension.'

Table 9.2 The functional bowel disorders. (From Thompson *et al.* [3].)

C	*Functional bowel disorders*
C1	**Irritable b wel syndrome**
C2	Functional abdominal bloating
C3	Functional constipation
C4	Functional diarrhea
C5	Unspecified functional bowel disorder

Table 9.3 Symptom criteria for IBS. (From Thompson *et al.* [3].)

At least 3 months of continuous or recurrent symptoms of:
- abdominal pain or discomfort that is:
  - (a) relieved with defecation, and/or
  - (b) associated with a change in frequency of stool, and/or
  - (c) associated with a change in consistency of stools

and:

- two or more of the following, during at least a quarter of occasions or days:
  - (a) altered stool frequency (defined here as more than three bowel movements per day or less than three per week)
  - (b) altered stool form (lumpy/hard or loose/watery stool)
  - (c) altered stool passage (straining, urgency, or feeling of incomplete evacuation)
  - (d) passage of mucus
  - (e) bloating or feeling of abdominal distention

Epidemiology

The IBS is very common. We [4] showed it to be present in 14% of British adults. Subsequent studies in the USA [5, 6], France [7], New Zealand [8], Denmark [9], and even China [10] indicate that such a prevalence rate is worldwide. Employing the Rome criteria, Drossman *et al.* [11] found the IBS to be present in 11.6% of respondents in a random sample of more than 8000 USA households. This study and a study [12] done in England indicate that IBS is twice as common in women as in men, but reports [9, 13] conflict as to a decreasing prevalence with age. These figures are sensitive to the definitions of IBS that are employed. In one instance [9], prevalence rates of 5–65% were found using different definitions. In a population survey [14], 38% of individuals who had had IBS by Manning and Rome criteria did not have it when surveyed 1 year later. However, about 9% who did not have IBS initially had acquired it. An even greater turnover was found over 5 years in that 95% had experienced some symptoms during that period [9].

Epidemiologic studies are hampered by a dependence on recall, which is notoriously flawed. For example, almost 40% of 961 adults with a previous fracture on their medical record had forgotten it when questioned 15 years later [15]. Most evidence suggests that IBS is a chronic relapsing disorder that probably occurs in most adults during their lifetime.

Most individuals reporting the IBS in population surveys do not seek medical help. Nevertheless, patients with the IBS constitute about 50% of those seen in Western [16] and Asian [17] clinics. Among Western clinic patients, women outnumber men by 3:1 or 4:1 [18, 19]. Curiously, in India and Sri Lanka, this ratio is reversed [20, 21]. Even though most IBS sufferers in the community do not consult a physician for their symptoms those who do present an important and costly health problem [4]. A management strategy must be developed with these facts in mind. There are indications that IBS patients seen by specialists are a subgroup of the whole, with psychosocial characteristics that are distinct from individuals with the same symptoms who do not seek medical care [22, 23] and probably distinct from IBS patients seen in primary care.

Prognosis

In terms of life expectancy, the prognosis of IBS is excellent. The symptoms are themselves benign, and there is no evidence that they predispose an individual to any other disorder. However, in terms of cure of symptoms, the outlook is not so good. Many studies [14, 24–28] confirm that despite a variety of treatments, most patients who receive a diagnosis of IBS still have symptoms when interviewed 1–10 years later. Given the fickleness of human memory, it is unlikely that many achieve a complete cure. In one survey [9], only 5% of IBS subjects interviewed at 5 years were completely free of symptoms. On the bright side, very few of these individuals had acquired an organic GI disease, and none seems to represent an original misdiagnosis.

Pathogenesis

Is IBS 'a qualitative or merely a quantitative departure from the psychophysiological reactions of healthy persons?' Thomas Almy [29].

The cause of IBS has confounded physicians for almost two centuries. Despite much research, we cannot even today offer a convincing explanation. Many hold strong beliefs. Some declare it is caused by something

in the diet. Others cite evidence to suggest that it is an infection, or are convinced that it is a motility disorder. Still others believe that it is due to altered perception, a psychological disorder, psychophysiologic phenomena, or even abnormal illness behavior. Perhaps all of these are true, or none are true, or some are true some of the time. Keep Professor Almy's question in mind. A condition affecting at least 11% of a physically healthy population may be no disease at all. Rather, the IBS may represent a normal response of the gut to its environment, made more or less prominent in an individual's consciousness by his or her fears or psychological state.

A dietary disorder?

Burkitt and his medical missionary colleagues [30] in East Africa noted that IBS, constipation, and other 'Western' bowel disorders were uncommon in natives consuming an indigenous high-fiber diet. In a 1972 study [30] of rural African and Westernized populations, they noted that the greater the dietary fiber content, the greater the daily stool weight and the shorter the whole-gut transit time. These facts led to the 'fiber hypothesis,' the concept that many diseases of the colon and other organs result from the ingestion of a Western, refined, low-fiber diet. By implication, IBS is one such disease.

Subsequent studies [31] confirm that a high-fiber diet increases stool bulk and shortens gut transit time. Many studies [32] attest to the value of bran, psyllium, and other bulking materials in the treatment of constipation. However, the presence of IBS has not been linked to an individual's fiber intake, and its presence in countries such as China [10] raises doubt that a single dietary factor such as fiber deficiency is at fault. A more telling source of doubt is the lack of success of dietary fiber supplements, such as bran and psyllium, in the treatment of IBS, as measured by double-blind trials [33]. Fiber may be a safe, cheap placebo, but it is not a cure. The fiber story is made even more confusing by the report [34] that among 'healthy' volunteers, an outgoing personality and a positive self-image predict a larger stool output. Nevertheless, there is evidence [35] that if at least 30 g of dietary fiber is taken daily, constipation and some other symptoms may improve.

Some patients are certain that a food substance is the culprit, if only that food could be identified. This pervasive idea has spawned irrational diets that defy science, cause much inconvenience, and even compromise nutrition. A true food allergy, such as to shellfish, affects systems beyond

the gut and is more likely to cause vomiting and diarrhea than IBS symptoms. Nonimmunoglobulin E (IgE)-mediated intolerances to wheat, dairy products, or beef are claimed to cause diarrhea in some cases, but not the IBS as strictly defined. Very few individuals with IBS can be confirmed by double-blind feedings to have a true food sensitivity [36]. It appears that this approach is likely to be useful only if the patient is suffering from diarrhea, but even that is disputed [36].

Certainly, a careful medical history should seek out evidence of lactose intolerance, excessive caffeine intake, use of sorbitol-containing gum, or other drug or dietary habits that may affect the gut [37]. Although a dietary factory may be involved in IBS in some individuals, it is unlikely to be the sole cause.

An infection or inflammation?

The IBS frequently follows an enteric infection [24, 28, 38]. Could IBS be, after all, an infection or an inflammation set up by an infection? Collins [39] suggests that cytokines emitted from submucosal mast cells or other inflammatory cells might cause the motility disturbances thought to occur in the IBS. Ileal mast-cell counts have been found to be greater in IBS patients than in controls [40]. On the other hand, rectal biopsies performed on 89 patients with the IBS as determined by established criteria and examined by blinded pathologists revealed no histologic difference between IBS patients and controls [41].

A motility disorder?

'[T]he bowels are at one time constipated, at another lax, in the same person.... How the disease has two such different symptoms I do not profess to explain...' W. Cumming [42].

Cumming's dilemma persists. Colon motility studies [43] in the 1960s suggested that in constipation, the motility index (frequency of contraction multiplied by amplitude of contraction) is increased. This holds up the passage of stool and causes abdominal pain. Conversely, this line of reasoning suggests that in those with diarrhea, the motility index is decreased. Here, the lax sigmoid permits liquid feces to trickle into the rectum, prematurely triggering defecation. But these observations have not turned out to be reliable features of constipation and diarrhea. Furthermore, it is now believed that the proximal colon and the small intestine are also dysfunctional in IBS [44–46]. In the 1970s, investigators

[47] reported that a 3-cycle per minute (cpm) myoelectric rhythm is more common in IBS patients than in controls. However, the specificity of this observation is doubted. Using a different technology, European workers [48] associated the recording of electrical short bursts in the colon with constipation and the lack of these bursts with diarrhea. In the 1980s, attention was drawn to the small bowel, where the secretory and motor responses to stress seem to be different in IBS patients than in normal individuals [44–46]. However, none of these phenomena is sufficiently specific to permit its use as a diagnostic test of IBS, nor indeed do any of them explain how the symptoms are generated.

Balloons inflated sequentially throughout the gut can identify trigger points that reproduce the abdominal pain experienced by most individuals with IBS [49, 50]. Even here, it is not certain to what extent the pain of IBS is a normal perception of abnormal physiology or an abnormal perception of normal physiology [51]. In IBS there is a tendency for both the small and large bowel to overreact to a variety of stimuli, such as drugs, stress, balloon distention, and even eating [47, 52, 53]. The last may represent an exaggerated gastrocolonic response [47]. Abnormalities in gut motility have yet to explain the diverse features of IBS.

A perception disorder?

The failure of motility observations to adequately explain IBS symptoms has led many to study the sensory or afferent connections between the gut and the brain. IBS patients appreciate pain at lower levels of rectal distention than do other individuals [53, 54], but they do not simply have a generalized low threshold for pain. Pain sensitivity as measured during electrocutaneous stimulation was similar in patients with either IBS or Crohn's disease, and both groups were less sensitive than were controls [55]. The autonomic connections between the enteric nervous system (ENS) and the central nervous system (CNS) are well known, and it is of further interest that the vagus and sympathetic nerves carry more afferent than efferent nerve fibers. 5-Hydroxytryptamine-3 (5-HT$_3$) and 5-HT$_4$ receptors may play an important role in transmitting impulses from the ENS to the CNS. Attempts are being made to develop antagonists to these receptors and thereby decrease gut sensitivity.

An individual's experience of pain may be greatly influenced by emotion, memory, culture, and psychosocial situation [56]. It is useful to distinguish acute pain from chronic pain [57]. Acute pain is linked to tissue pathology or organ dysfunction and, in the case of the gut, is

associated with eating, defecation, and vomiting. Chronic pain is continuous and unassociated with physiologic responses to pain, such as sweating and tachycardia. The patient with chronic pain is often depressed, and there may be secondary gain or prior adverse experiences such as sexual abuse and threatening life events.

The perception of pain varies from patient to patient. Acute, function-related pain is primarily sensory or peripheral and may lend itself to treatment with analgesics directed at the organ involved. Chronic pain, which is influenced more by CNS controlling activity, may require treatment directed at behavior that is influenced by emotion or cognition. Drugs such as the tricyclic antidepressants enhance the production of 5-HT and inhibit pain impulses, thereby reducing the perception of noxious stimuli [58]. They may also enhance endorphin release. In contrast, benzodiazepines carry a risk of habituation, and via gamma-aminobutyric acid (GABA) production, they may inhibit the production of 5-HT and increase pain perception [59].

It is not only pain that may be misperceived by patients. They often misinterpret their bowel action as well [60]. Although stool frequency in the population ranges from three movements per week to three per day, many consider variations within this range to be abnormal. Others misinterpret frequent but hard, fragmented, or lumpy stool as diarrhea when, in fact, gut transit is prolonged. Heaton and O'Donnell [61] have termed this 'pseudodiarrhea.' Patients often complain of symptoms such as borborygmi, flatus, and distention, giving little indication that these symptoms are objectively different from those in noncomplainers. Lasser et al. [62] found that patients complaining of 'gas' or 'bloating' had no excess intestinal gas.

Clearly, how sensory input is perceived is an important determinant of the IBS. Acute, function-related symptoms need to be treated differently from symptoms that are chronic, continuous, and associated with psychosocial distress [56]. Nonetheless, perception alone does not explain the altered gut function, nor does it seem important in those with IBS symptoms who do not seek medical care.

A psychological disorder?

The notion that IBS symptoms are interrelated with, perhaps even caused by, an individual's psychological state is as old as the concept of IBS itself. Many studies [22, 23, 63, 64] attest that anxiety, depression, and other forms of psychological distress are more likely in IBS patients than in

patients with organic disease. However, the patients in these studies were in a tertiary care setting and thus unlikely to be representative of all persons experiencing IBS symptoms. Whitehead *et al.* [23] and Drossman *et al.* [22] found that the psychosocial makeup of IBS sufferers in the community who do not see doctors is the same as that of normal individuals. It also appears that IBS and psychosocial distress, when they do occur in the same patient, are not necessarily concurrent [65, 66]. In one British clinic, chronic attendees with IBS were compared with newly referred patients [67]. Although psychological morbidity was similar in the two groups, the social consequences in the chronic attendees were more severe. There are no studies of the psychological state of IBS patients seen in primary care, but these patients are likely to represent an intermediate population.

The foregoing data do not support the notion that psychopathology *causes* the IBS. Indeed, antidepressants are most effective in IBS patients without psychopathology [68]. Perhaps a psychopathological condition worsens IBS symptoms or elevates them to the status of a medical problem in a person's consciousness (a perception disorder?). Could psychological distress be a determinant of health-care seeking? For the emotionally troubled person, IBS symptoms provide a socially acceptable vehicle for care.

These arguments are reinforced by observations [69] that IBS patients tend to seek medical care after a stressful or threatening life event. At the simplest level, a man with IBS who has ignored his symptoms for years may become acutely aware of them when a close relative succumbs to cancer. Compared with age- and less sex-matched controls, IBS patients commonly express concerns about cancer to their doctor [70]. Here, treatment is obvious. Reassure the patient that he or she does not have cancer; further treatment is usually unnecessary.

The management of patients whose visits appear to be precipitated by depression, job loss, marital breakup, or other personal catastrophe may be much more complicated. Many tertiary care patients are polysymptomatic, complaining of fatigue and headache [71, 72]. Others have suffered sexual or physical abuse [73]. In such situations, treatment that focuses on the gut symptoms may be misplaced.

A psychophysi logic disorder?

It is the common experience that emotion affects gut function. Who has not suffered some gut upset before an exam, a marriage, a death, or

another stressful or emotional event? In the early 1950s, Almy [74] demonstrated that stress could alter gut motility but that the changes were not specific to the stress. One person may have 'butterflies,' another diarrhea, another vomiting, and yet another a migraine. It seems that a given emotion may elicit different responses at different times in different persons. Perhaps these responses can be learned in early childhood [75]. In the IBS the relationship of symptoms to stress is more subtle. Changes in stress may be important. Some even notice that symptoms improve during a crisis, only to return later.

In IBS patients, the gut appears to be more reactive to a variety of stimuli when compared with controls. Drugs [76], hormones [77], food [52], distention [53, 78], and emotional stress [79] elicit exaggerated motor responses. An air insufflation test has been suggested [80] for IBS. Using radiotelemetry equipment, Valori *et al.* [79] observed that motility of the small bowel was altered in a different manner in IBS patients than in controls. He and his colleagues employed such stressors as heavy metal music, nocturnal arousal, and parking in London traffic to challenge the small bowel. It seems certain that stresses may nonspecifically alter gut function, and the alterations seem to be different in IBS patients. What determines these reactions? Are they clues to the cause of IBS, or are they merely epiphenomena?

A behavioral disorder?

Compared with persons with peptic ulcer, those with IBS have more somatic symptoms, view colds and flu more seriously, and consult physicians more frequently for minor complaints [75]. As children, they also were more likely than others to have received gifts or remained home from school when ill. These data support the notions that persons with IBS are prone to chronic illness behavior and that this behavior is learned.

Health-care seeking in the IBS, particularly at tertiary care centers, may be due as much to a person's cultural and psychosocial states as to the IBS symptoms themselves. How else can one explain why women are more likely than men to take their IBS symptoms to a doctor in Western cultures, while the opposite is true in India [4]? Why do only a minority of those with the IBS seek medical attention? The concurrence of threatening life events and psychosocial distress may partially explain these phenomena.

An integrated view

It must be evident from the foregoing that purely mechanistic or purely psychological explanations of IBS are inadequate reconciliations of the available facts. The physician should weigh all the considerations presented here as he or she interviews a patient (Figure 9.1). Evaluation of the relative importance of diet, disordered physiology, misperceptions, psychosocial maladaptations, and altered behavior in a patient may be as important to management as the establishment of a correct diagnosis. Past experience with diagnosing and treating peptic ulcers should make us cautious about accepting any of the current hypotheses. There, the focus on either acid secretion or psychosomatics as the cause blinded us to other possibilities and made it difficult to accept the role of *Helicobacter pylori.*

Noone's gut functions perfectly all the time, and variation in the population is great. Whatever the underlying pathophysiology, some people ignore the symptoms, while others permit the symptoms to dominate their lives. This variability is undoubtedly influenced by the emotions and life events that buffet us all. Further complicating the matter are human behavior, subtly learned in early childhood, and the negative incentives of Western social welfare systems. Since cure is elusive and we can do little to change life situations, the objective of IBS treatment should be improved functioning.

A therapeutic approach

Despite the reality that the pathogenesis of IBS is unknown, we have learned much about its epidemiology, prognosis, and diagnosis. The task
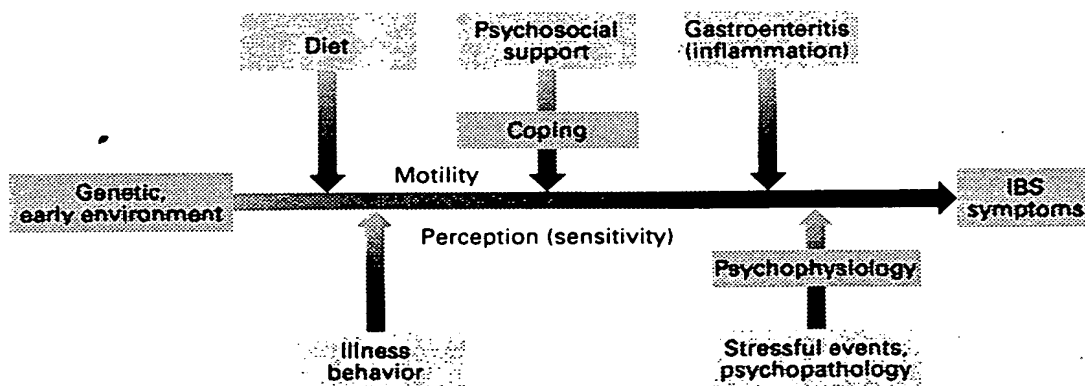
Fig. 9.1 Pathogenesis of IBS.

is to develop a strategy of management based on the known facts. Such a strategy should rely on six principles:

1   a positive diagnosis;
2   consideration of the patient's agenda;
3   critical appraisal of drugs and placebos;
4   the use of dietary fiber;
5   continuing care;
6   a graded therapeutic response.

A positive diagnosis

A careful history and physical examination permit a confident diagnosis that stands up over time. Physicians who consider the IBS a diagnosis of exclusion feel compelled to exclude all organic disease. This approach is expensive, especially if extrapolated to the many patients who seek medical care. The physician should attempt to establish a positive diagnosis at the first clinical encounter [3, 37, 56]. This is usually possible using the criteria shown in Table 9.3. A condition that affects up to 20% of the population is bound to coexist with organic disease in some. Therefore, one should inquire about symptoms such as anemia, bleeding, fever, weight loss, or a recent change in bowel habit.

If such symptoms and physical findings are absent, the investigation should be minimal. A sigmoidoscopy should be performed, but biopsy in search of microscopic colitis in the absence of continuous diarrhea is an unnecessary expense [41]. If the patient is older than 40 years of age or has risk factors for colon carcinoma, a barium enema is prudent. Even though the symptoms of the IBS are not those of polyp or cancer, a 'clean colon' is a reassuring start for all concerned. Other tests should be avoided unless indicated. An early, confident diagnosis permits tests to be minimized and reassures the patient that there is no mortal disease. Especially since fear of cancer is so common among IBS patients [70], such reassurance may be the physician's most effective therapeutic weapon.

The patient's agenda

Most persons with the IBS do not consult doctors. Those who do may have reasons for the visit beyond the gut. Severity of symptoms may be important, but psychosocial factors must also affect the decision. The answer to the question 'Why has this patient come to see the doctor now?' may be an important therapeutic clue. Fear of serious disease should be

met by firm reassurance that none exists. Threatening life events, whether they precipitate the IBS or the consultation, should be discussed. Some patients may require psychological help or stress management expertise, but simple supportive psychotherapy by the attending physician may be salutary. In a Swedish study [81], IBS patients treated with eight sessions of supportive psychotherapy, which could be performed in any physician's office, had fewer symptoms and less psychological and physical disability, compared to a control group, when they were seen 3 months later. The improvement was even more marked 1 year later. This supports the notion that early, careful attention to the patient's psychosocial concerns has effective and lasting benefit. Such an approach is supported by an English study [82], which also noted that improvement is most likely if psychopathology is recognized and dealt with and the pain is not constant.

Drugs and placebos

'[N]ot a single study has been published that provides compelling evidence that any therapeutic agent is efficacious in the global treatment of IBS.' K.B. Klein [83].

There are too many clinical trials of drugs in IBS to report here. The reader is referred to Klein [83], who reviewed controlled trials conducted over a 20-year period and found them all flawed. The entry criteria are usually unclear, and the symptom criteria of Manning [84], Kruis [85], and the Rome teams [3] are recent innovations. Many studies are too small or too short, or have too many dropouts. Others have an inappropriate trial design or use improper statistics. Thus, no drug has been proven to be globally effective in treating IBS.

Although trial methodology is improving, studies subsequent to Klein's critique are still inadequate. An international working team [86] agreed with and updated Klein's conclusions and set out suggested standards for clinical trials. One meta-analysis [87] examined randomized controlled trials of smooth-muscle relaxants and concluded that five such drugs showed 27% and 19% improvements over placebo in global assessment and pain, respectively. However, only 26 of 148 known trials were selected, and abstracts and letters were discarded. Since it is likely that some trials failed to appear at all, a publication bias must be suspected. Even with negative studies possibly excluded, the benefits seem marginal at most. IBS is a benign disorder that affects up to 20% of adults through long periods of their lives. Physicians should discourage the

chronic use of costly, systemic drugs of doubtful benefit, which in some cases may have unwanted consequences that can be more troublesome than the IBS itself.

Nevertheless, amid the rigors of science, there is a place for common sense in the use of drugs to treat the symptoms of IBS (Table 9.4). If diarrhea is the dominant symptom, with urgency, even incontinence, loperamide (Imodium®) may be helpful. This drug not only slows gut motility and decreases small bowel secretion but also increases anal sphincter strength [88]. Unlike other opiates, it does not enter the brain. Provided the diarrhea is genuine and not pseudodiarrhea [61], and reactive constipation does not result, such a drug can target the most troublesome symptom for a few patients. Other examples of such targeted therapy include bran or psyllium for constipation [33], avoidance of vegetables in the cabbage family, and perhaps use of alpha-D-galactosidase (Beano®) for excessive flatus, and a preprandial anticholinergic agent for abdominal pain that occurs after meals [47].

Anxiety and depression must be treated on their own merits. Treatment of psychological distress may permit a patient to cope better with IBS symptoms. In some pain-dominant IBS patients, tricyclic antidepressants may be helpful even if depression is not obvious [65, 66, 89]. These drugs have proven effective in other chronic pain syndromes [90] and may act via central pathways that influence the perception of pain. They seem to be effective at low doses and before any change in mood

Table 9.4 Drugs useful for certain difficult IBS symptoms. (From Thompson [37].)

Indication	Drug	Maximum dose
Diarrhea-dominant IBS	Loperamide (Imodium®)	1–2 tablets three times daily
	Cholestyramine (Questran®)	1 teaspoonful (4 g) three times daily
Pain-dominant IBS Postmeal pain [47] Chronic pain syndrome [68]	Dicyclomine (Bentyl®) Amitriptyline (Elavil®)	10–20 mg before meals 25 mg at bedtime, with increments to 100 mg
Constipation	Bran or psyllium	1 tablespoonful three times daily with meals, and adjust
Gas/bloat/flatus	Alpha-D-galactosidase (Beano®) Simethicone	— 1–2 tablets three times daily

occurs. A recommended starting dose of amitriptyline (Elavil⁸) is 25 mg at bedtime, with increments every 4–5 days until benefit is achieved. The dose seldom exceeds 100 mg, but anticholinergic or sedating side effects may necessitate switching to another drug, such as doxepin (Sinequan⁸).

An important feature of IBS symptoms is the tendency to improve with placebo. In existing therapeutic trials, the placebo response ranges from 40 to 70% [37]. There are lessons to be learned from this placebo response.

1 It demonstrates the variability of the disease, which tends to improve with time.

2 It supports the contention that no drug is generally acceptable for IBS patients without convincing demonstration of efficacy in defined-entry, randomized, placebo-controlled, double-blind clinical trials.

3 Placebos may be useful in certain circumstances. It is said that if a placebo is to have a therapeutic effect, the patient must believe that it will. Nevertheless, in a group of neurotic patients, placebo was effective even when they knew the pills were inert [91]. It seems that the symbolic giving of medication has a therapeutic value. Logical placebos that have a plausible rationale, yet are inexpensive and safe, may exploit these phenomena.

4 The most important implication of the placebo response is that it demonstrates the beneficial effect of a successful physician–patient encounter.

Dietary fiber

Although bran, psyllium, and dietary fiber are not proven effective in the treatment of IBS [33, 92, 93], they should still be tried by the primary care doctor. Fiber is effective in constipation and pseudodiarrhea. Ingestion of sufficient fiber has a visible effect on stool form and is a cheap, safe method of eliciting the placebo response. It also involves the patient in his or her own care in a way that passive ingestion of a pill may not. Fiber needs to be taken in sufficient doses. To encourage compliance and more easily titrate the dose of fiber, the author prefers to have the patient take three tablespoonsful three times a day with meals and adjust the amount according to its effect on the stool. There are reports of intolerance to bran in patients at tertiary care centers, but such patients have usually tried bran and failed [94, 95]. Specialists are less likely to achieve success with fiber in their selected patients than a primary care physician encountering a patient for the first time. If bran works, referral becomes redundant.

Continuing care

Cure, or even acceptance of the diagnosis, is an unrealistic goal for some troubled IBS patients. Unsatisfied with their doctor, they are prone to turn to practitioners of alternative medicine [96, 97]. Some diets and remedies recommended by these sources are inappropriate, even harmful, and important intervening disease may be overlooked. It is, therefore, important that the physician assure the patient of the availability of continuing care.

Emotionally disturbed patients benefit from regular, brief visits. These visits offer reassurance, and control 'doctor-shopping' and inappropriate ordering of tests and treatments. Through such visits, the doctor can be vigilant for a change in symptoms. Assistance may be sought from psychologists, psychiatrists, or other services if needed. Some patients may benefit from a stress management program. Patients with severe symptoms may require the multidisciplinary services of a pain clinic. Although biofeedback [98] and hypnosis [99] seem to benefit some patients, such services are not available in many cities. If the physician seems to lose the confidence of a patient, referral to an esteemed colleague may help by confirming the diagnosis and reinforcing the management plan.

A graded therapeutic response [56]

The therapeutic response must be tailored to the individual needs of IBS sufferers if we are to use our resources economically and effectively. Most individuals with the IBS do not seek medical attention. Many who do consult a primary care physician are worried about the meaning of their symptoms and will likely respond to explanation and reassurance. Those who return with the same symptoms or who are referred to specialists may require more attention. Those who chronically seek help from sub-specialists are a small, unhappy, but costly subgroup in whom psychosocial factors may be more disabling than the gut symptoms themselves.

The primary care physician should emphasize the positive diagnosis, the chronic yet benign nature of the symptoms, the role of stress, and the inutility of drugs. Bulk, such as bran, improves constipation and is otherwise a safe, cheap placebo. For nonresponders, once the foregoing items have been dealt with satisfactorily, supportive psychotherapy and drugs for specific indications may be added. Overinvestigation or re-peated testing and referral without substantial indication may undermine the patient's confidence in the doctor's conclusions. The emphasis should

be directed toward improved daily functioning. There may be a role for special treatments such as stress management, psychotherapy, behavioral modification, or a psychotherapeutic agent such as amitriptyline. In the end, there is no substitute for the ongoing support of a caring family doctor.

Summary

The cause of the IBS is unknown, but it is very common in the community. Most sufferers do not see doctors. There is evidence that factors other than symptoms contribute to the decision to seek medical care. Examination of these factors not only suggests that the cause is multifactorial, but also offers clues for the management of individual patients. There is either some evidence for, or strong belief in, the importance of diet, inflammation, disordered motility, psychophysiology, or psychopathology in the genesis of the IBS. It seems that severe life events and an altered perception of symptoms may also be important and that several factors may act in concert to induce illness behavior. In some patients, all factors may be present; in others, apparently none. But the more factors are at work, the more complex the treatment.

Management should take advantage of the known features of the disease. Its prevalence, recognizable symptoms, and benign nature indicate the reassurance value of a positive diagnosis. The tendency of patients, especially chronic complainers, to have psychopathology or antecedent stressful life events may indicate important management issues. Although drugs are unproved in the global treatment of IBS, certain agents may benefit specific symptoms and may also employ the placebo response to advantage. Insecure patients or chronic complainers need continuing care. Different levels of disability require a graded treatment response to IBS complaints. This implies reassurance and drug-free management at the primary care level, with increments of psychosocial support and specific use of drugs in nonresponders. The goal of therapy in severe, intractable cases should be improved functioning rather than cure.

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